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Commentary

Prevention of Atherosclerotic Cardiovascular Disease

What Is the Best Approach and How Early Should We Start?

Stephen R. Daniels, MD, PHD

Aurora, Colorado

After decades of research, there is no question that atherosclerosis begins early in life and is progressive, ultimately leading to the cardiovascular outcomes of coronary heart disease and cerebrovascular disease in adult life (1). It is also clear that there are important risk factors that, when present, increase the risk of adverse outcomes (2). These risk factors include elevated low-density lipoprotein cholesterol (LDL-C), low high-density lipoprotein cholesterol, hypertension, diabetes mellitus, cigarette smoking, and obesity. The recently published American College of Cardiology (ACC)/American Heart Association (AHA) guidelines on prevention of atherosclerotic cardiovascular disease (ASCVD) in adults emphasizes understanding the level of risk based on risk factors and, when appropriate, implementing evidence-based lifestyle and pharmacological treatment to prevent adverse cardiovascular outcomes (3,4). An important advance in these new guidelines is that they are based not on evidence related to reduction of intermediate outcomes, such as levels of risk factors, but on evidence related to the prevention of important health outcomes, such as coronary events and stroke (5).

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Although this is an important advance for the prevention of ASCVD in adults, it leaves open the question of prevention of adverse cardiovascular outcomes starting in childhood and adolescence. The ACC/AHA Guideline on the Assessment of Cardiovascular Risk makes it clear that, although the concept of lifetime risk is important, at present, the existing data only support an approach to estimating 10-year risk of ASCVD (3). They concluded that long-term and lifetime risk information may be used most appropriately to motivate therapeutic lifestyle modification in younger individuals at lower 10-year risk, but evidence is lacking for long-term and lifetime risk assessment to be used in guiding decisions regarding pharmacological therapy in the prevention of ASCVD.

The concept of lifetime risk remains important, however. Evidence from observational studies demonstrates that individuals who maintain a low-risk profile, including normal blood pressure, normal body mass index, normal total cholesterol, no diabetes, and no cigarette smoking through childhood, adolescence, and young adulthood up to 50 years of age have an exceedingly low risk of subsequent ASCVD and a substantially longer life expectancy (6). Additional data from these observational studies demonstrate that although genetics plays some role in the ability to maintain low-risk status, much of this favorable status is achieved by maintaining an optimal cardiovascular lifestyle or health factors throughout early life (7).

With this background, in this issue of the *Journal*, Robinson and Gidding (8) present an argument for a very early and very aggressive approach, including aggressive pharmacological intervention to "cure" atherosclerosis and therefore prevent ASCVD. They propose a very early moderate-intensity statin LDL-C–lowering strategy in children and adolescents and an early, very aggressive LDL-C–lowering strategy in young adults, including the use of statins and possibly other lipid-lowering agents. In support of this strategy, they present several lines of evidence. Some of the evidence comes from observational studies of children and adolescents, some from the limited clinical trials in children and adolescents, and additional evidence from clinical trials of adults. Important evidence from adult clinical trials includes the legacy effect of intervention with statins that favor the intervention over the placebo group as long as 10 years after the trial has been completed. Presumably, both groups are treated with the intervention (statins) thereafter, but the intervention group continues to have a lower rate of events (9).

Although the approach suggested by Robinson and Gidding (8) has some evidence to support it, and it may present hypotheses to be tested in future trials, it also has substantial gaps in the supportive evidence and problems with any real-life strategy to implement their approach. The

From the Department of Pediatrics, University of Colorado School of Medicine, Children's Hospital Colorado, Aurora, Colorado. Dr. Daniels has reported that he has no relationships relevant to the contents of this paper to disclose.

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first concern is theoretical. They present the approach as a "vaccination" and "cure." It is not clear that the analogy to vaccinations is useful in the context of atherosclerosis. Vaccination to prevent infectious disease has a strong biological underpinning related to the creation of a pre-emptive biological immune response, which can then prevent infection when there is future exposure to the infectious agent. This does not appear to be operative in the prevention of atherosclerosis and ASCVD. It is also unclear that atherosclerosis can be "cured."

Another important concern behind this entire discussion is that we currently have no methods to image and evaluate the presence and progression of the atherosclerotic process, particularly the early stages of this process. This is 1 reason why, historically, we have been forced to focus on risk factors, which can be measured and followed. However, as Psaty and Weiss (5) have noted, management of risk factors does not always relate directly to prevention of ASCVD. Robinson and Gidding (8) propose that carotid intima-media thickness (CIMT) is the best noninvasive measure for assessing atherosclerosis. However, the ACC/AHA risk assessment guidelines specifically indicate that CIMT is not recommended for routine measurement for clinical practice for adults (3). Even if CIMT were to be recommended, it should be remembered that it is a surrogate measure, not a direct measure, of atherosclerosis in the coronary or cerebral arteries.

Another concern is that Robinson and Gidding (8) are not very specific about how their proposed approach would be implemented in practice. They mention patients with heterozygous familial hypercholesterolemia, which is a group at high lifetime risk of ASCVD (10). They also mention young patients with type 2 diabetes mellitus, which is another group that appears to be at high lifetime ASCVD risk (11). However, they also mention young patients with obesity, insulin resistance, pre-hypertension, elevated triglycerides, and low high-density lipoprotein cholesterol. The lifetime risk of ASCVD is much less clear in these patients, and the balance between potential benefits and risks of very aggressive intervention may be substantially less favorable. It is also not clear at which age they would propose to initiate the aggressive intervention and if the intervention is to be intermittent rather than continuous, how long the intervention would last, and how one would determine whether it was effective.

So, where does this leave us in practical terms? It is clear that a deeper evidence base regarding the initiation of atherosclerosis in childhood and the role of risk factors and their progression over time is needed. Better measures of atherosclerosis via imaging would provide a tremendous advance. Some of the needed evidence will come from observational studies, but better clinical trials of the safety and efficacy of lifestyle and pharmacological intervention with appropriate duration and outcomes will also be needed. Studies will need to span the age ranges from risk factor development in childhood to important health outcomes in adulthood. However, it must be recognized that such long-term studies are very difficult to perform and do not provide meaningful answers for decades. In the meantime, we need to develop useful approaches to calculating long-term risk of ASCVD in young people.

Although the evidence base continues to develop, the Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents continue to provide the best evidence-based approach to the evaluation and management of risk for ASCVD in young individuals (12). These guidelines focus on understanding the health impact of the entire constellation of cardiovascular disease risk factors. They focus on primordial prevention of risk factors through adoption of lifelong healthy behaviors. For those children and adolescents in whom risk factors emerge, the focus is on more intensive lifestyle intervention to promote a healthful diet and levels of physical activity. Consideration of more aggressive pharmacological intervention is reserved for a very small proportion of children who are deemed to be at very high risk, usually because of genetic abnormalities, leading to quite high levels of risk factors.

Robinson and Gidding (8) should be commended for a piece that provokes thought and provides hypotheses to be tested in future research. However, current clinical practice should be grounded in the best current evidence regarding efficacy and safety (12).

Reprint requests and correspondence: Dr. Stephen R. Daniels, Children's Hospital Colorado, 13123 East 16th Avenue, B065, Aurora, Colorado 80045. E-mail: Stephen.Daniels@childrenscolorado.org.

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